kinase α subunit mutations. In contrast, CIS and invasive tumors have a higher frequency of *TP53* and *RB* gene alterations. Within all clinical stages, including Tis, T1, and T2 or greater lesions, tumors with alterations in *p53*, *p21*, and/or *RB* have a higher probability of recurrence, metastasis, and death from disease.

CLINICAL PRESENTATION, DIAGNOSIS, AND STAGING

Hematuria occurs in 80–90% of patients and often reflects exophytic tumors. The bladder is the most common source of gross hematuria (40%), but benign cystitis (22%) is a more common cause than bladder cancer (15%) (Chap. 61). Microscopic hematuria is more commonly of prostate origin (25%); only 2% of bladder cancers produce microscopic hematuria. Once hematuria is documented, a urinary cytology, visualization of the urothelial tract by computed tomography (CT) or magnetic resonance urogram or intravenous pyelogram, and cystoscopy are recommended if no other etiology is found. Screening asymptomatic individuals for hematuria increases the diagnosis of tumors at an early stage but has not been shown to prolong life. After hematuria, irritative symptoms are the next most common presentation. Ureteral obstruction may cause flank pain. Symptoms of metastatic disease are rarely the first presenting sign.

The endoscopic evaluation includes an examination under anesthesia to determine whether a palpable mass is present. A flexible endoscope is inserted into the bladder, and bladder barbotage for cytology is performed. Visual inspection includes mapping the location, size, and number of lesions, as well as a description of the growth pattern (solid vs papillary). All visible tumors should be resected, and a sample of the muscle underlying the tumor should be obtained to assess the depth of invasion. Normal-appearing areas are biopsied at random to ensure no CIS is present. A notation is made as to whether a tumor was completely or incompletely resected. Selective catheterization and visualization of the upper tracts should be performed if the cytology is positive and no disease is visible in the bladder. Ultrasonography, CT, and/or magnetic resonance imaging (MRI) are used to determine whether a tumor extends to perivesical fat (T3) and to document nodal spread. Distant metastases are assessed by CT of the chest and abdomen, MRI, or radionuclide imaging of the skeleton.

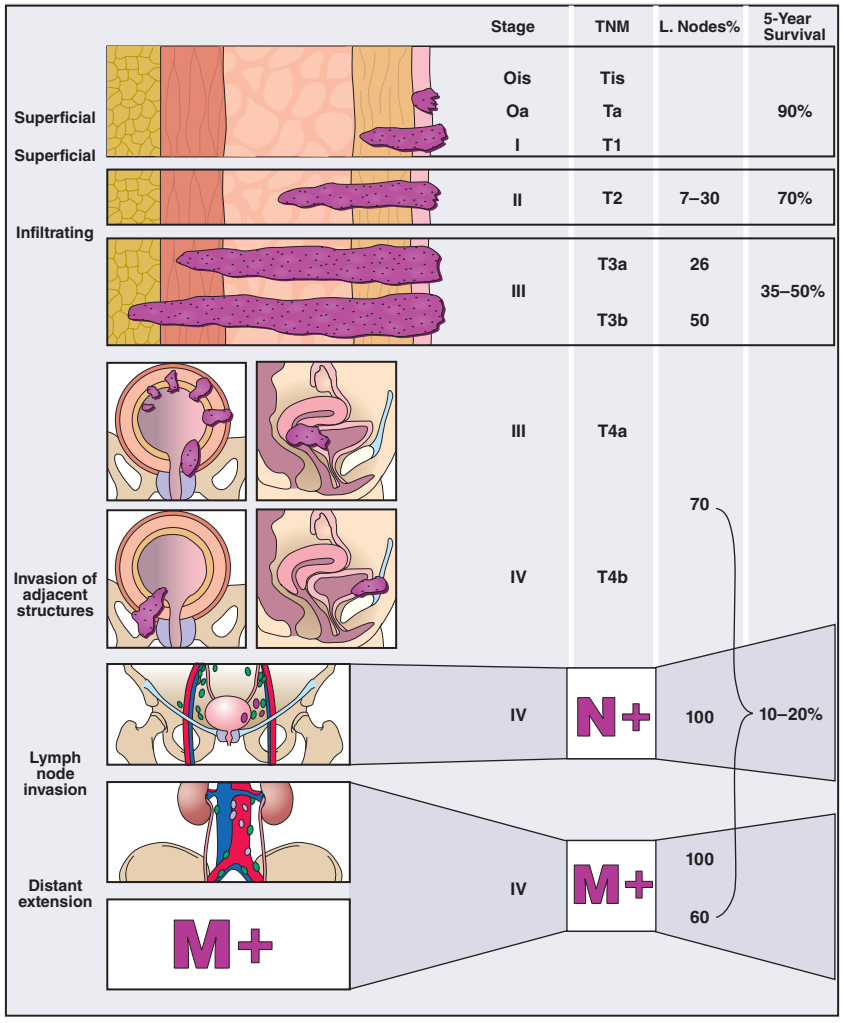

FIGURE 114-1 **Bladder staging.** TNM, tumor, node, metastasis.

TREATMENT BLADDER CANCER

Management depends on whether the tumor invades muscle and whether it has spread to the regional lymph nodes and beyond. The probability of spread increases with increasing T stage.

NON–MUSCLE-INVASIVE DISEASE

At a minimum, the management is complete endoscopic resection with or without intravesical therapy. The decision to recommend intravesical therapy depends on the histologic subtype, number of lesions, depth of invasion, presence or absence of CIS, and antecedent history. Recurrences develop in upward of 50% of cases, of which 5–20% progress to a more advanced stage. In general, solitary papillary lesions are managed by transurethral surgery alone. CIS and recurrent disease are treated by transurethral surgery followed by intravesical therapy.

Intravesical therapies are used in two general contexts: as an adjuvant to a complete endoscopic resection to prevent recurrence or to eliminate disease that cannot be controlled by endoscopic resection alone. Intravesical treatments are advised for patients with diffuse CIS, recurrent disease, >40% involvement of the bladder surface by tumor, or T1 disease. The standard therapy, based on randomized comparisons, is Bacillus Calmette-Guérin (BCG) in six weekly instillations, often followed by maintenance administrations for ≥1 year. Other agents with activity include mitomycin C, interferon, and gemcitabine. The side effects of intravesical therapies include dysuria, urinary frequency, and, depending on the drug, myelosuppression or contact dermatitis. Rarely, intravesical BCG may produce a systemic illness associated with granulomatous infections in multiple sites requiring antituberculin therapy.

Following the endoscopic resection, patients are monitored for recurrence at 3-month intervals during the first year. Recurrence may develop anywhere along the urothelial tract, including the renal pelvis, ureter, or urethra. Persistent disease in the bladder and new tumors are treated with a second course of BCG or intravesical chemotherapy with valrubicin or gemcitabine. In some cases, cystectomy is recommended. Tumors in the ureter or renal pelvis are typically managed by resection during retrograde examination or, in some cases, by instillation through the renal pelvis. Prostatic urethral tumors may require cystoprostatectomy if the tumor cannot be resected completely.

MUSCLE-INVASIVE DISEASE

The treatment of a tumor that has invaded muscle can be separated into control of the primary tumor and systemic chemotherapy to treat micrometastatic disease. Radical cystectomy is the standard treatment in the United States, although in selected cases, a bladder-sparing approach is used. This approach includes complete endoscopic resection; partial cystectomy; or a combination of resection, systemic chemotherapy, and external beam radiation therapy. In some countries, external beam radiation therapy is considered standard. In the United States, it is generally limited to those patients deemed unfit for cystectomy, those with unresectable local disease, or as part of an experimental bladder-sparing approach.